Notice of Allowability	Application No.	Applicant(s)	
	10/076,840	MURPHY ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *2/6/06*.

2. ☒ The allowed claim(s) is/are *79-86 and 88-94*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Valeta Gregg on May 9, 2006.

The application has been amended as follows:

1. Replace claim 79 with the following:

79. A method of creating, in an isolated mouse embryonic stem (ES) cell, a genetically modified endogenous gene locus flanked downstream by a site-specific recombination site comprising:

(a) using bacterial homologous recombination to genetically modify a cloned genomic fragment of an endogenous gene locus to create a large targeting vector for use in eukaryotic cells (LTVEC), said LTVEC comprising a site-specific recombination site, a downstream homology arm containing a region homologous to the 3' end of the endogenous gene locus region and an upstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511, and lox2272;

(b) introducing the LTVEC of (a) into an isolated mouse ES cell; and

(d) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous gene locus of the cell, wherein the

endogenous gene locus is flanked downstream by the site-specific recombination site.

2. Replace claim 80 with the following:

80. A method of creating, in an isolated mouse embryonic stem (ES) cell, a genetically modified endogenous gene locus flanked upstream by a site-specific recombination site comprising:

(a) using bacterial homologous recombination to genetically modify a cloned genomic fragment of an endogenous gene locus to create a large targeting vector for use in eukaryotic cells (LTVEC), said LTVEC comprising a site-specific recombination site, an upstream homology arm containing a region homologous to the 5' end of the endogenous gene locus region and a downstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511, and lox2272;

(b) introducing the LTVEC of (a) into an isolated mouse ES cell; and

(c) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous gene locus of the cell, wherein the endogenous gene locus is flanked downstream by the site-specific recombination site.

3. Replace claim 81 with the following:

81. A method of creating, in an isolated mouse embryonic stem (ES) cell, a genetically modified endogenous gene locus flanked by site-specific recombination sites comprising:

(a) using bacterial homologous recombination to genetically modify a cloned genomic fragment of an endogenous gene locus to create a first large targeting

vector for use in eukaryotic cells (LTVEC), said LTVEC comprising a site-specific recombination site, a downstream homology arm containing a region homologous to the 3' end of the endogenous gene locus region and an upstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511, and lox2272;

(b) using bacterial homologous recombination to create a second LTVEC comprising the site-specific recombination site, an upstream homology arm containing a region that flanks the 5' end of the endogenous gene locus region and a downstream homology arm within the locus;

(c) introducing the first and second LTVECs into an isolated mouse ES cell; and

(d) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (c) thereby indicating modification of allele (MOA) in the endogenous gene locus of the cell, wherein the site-specific recombination sites are flanking the endogenous gene locus.

4. Replace claim 88 with the following:

88. A method of creating, in an isolated mouse embryonic stem (ES) cell, a genetically modified endogenous immunoglobulin variable region gene locus flanked downstream by a site-specific recombination site comprising:

(a) using bacterial homologous recombination to genetically modify a cloned genomic fragment of an endogenous immunoglobulin variable region gene locus to create a large targeting vector for use in eukaryotic cells (LTVEC), said LTVEC comprising a site-specific recombination site, a downstream homology arm containing a region homologous to the 3' end of the endogenous immunoglobulin variable gene locus region and an upstream homology arm within the locus,

wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511, and lox2272;

(b) introducing the LTVEC of (a) into an isolated mouse ES cell; and

(c) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous immunoglobulin variable region gene locus of the cell, wherein the endogenous immunoglobulin variable region gene locus is flanked downstream by the site-specific recombination site.

5. Replace claim 89 with the following:

89. A method of creating, in an isolated mouse embryonic stem (ES) cell, a genetically modified endogenous immunoglobulin variable region gene locus flanked upstream by a site-specific recombination site comprising:

(a) using bacterial homologous recombination to genetically modify a cloned genomic fragment of an endogenous immunoglobulin variable region gene locus to create a large targeting vector for use in eukaryotic cells (LTVEC), said LTVEC comprising a site-specific recombination site, an upstream homology arm containing a region homologous to the 5' end of the endogenous immunoglobulin variable gene locus region and a downstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511, and lox2272;

(b) introducing the LTVEC of (a) into an isolated mouse ES cell; and

(c) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (b) thereby indicating modification of allele (MOA) in the endogenous immunoglobulin gene locus of the

cell, wherein the endogenous gene locus is flanked downstream by the site-specific recombination site.

6. Replace claim 90 with the following:

90. A method of creating, in an isolated mouse embryonic stem (ES) cell, a genetically modified endogenous immunoglobulin variable region gene locus flanked site-specific recombination sites comprising:

(a) using bacterial homologous recombination to genetically modify a cloned genomic fragment of an endogenous immunoglobulin variable region gene locus to create a first large targeting vector for use in eukaryotic cells (LTVEC), said LTVEC comprising a site-specific recombination site, a downstream homology arm containing a region homologous to a 3' end of the endogenous immunoglobulin variable gene locus region and an upstream homology arm within the locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511, and lox2272;

(b) using bacterial homologous recombination to genetically modify a cloned genomic fragment of an endogenous immunoglobulin variable region gene locus to create a second LTVEC comprising a site-specific recombination site, an upstream homology arm containing a region that flanks the 5' end of the endogenous immunoglobulin variable region gene locus region and a downstream homology arm within the locus;

(c) introducing the first and second LTVECs into an isolated mouse ES cell; and

(d) using a quantitative assay with a probe directed to an unmodified allele of the endogenous immunoglobulin variable region gene locus to detect reduced copy number of the unmodified allele compared to that of a reference gene in the cell from (c) thereby indicating modification of allele (MOA) in the endogenous gene

locus of the cell, wherein the endogenous gene locus is flanked downstream by the site-specific recombination site.

7. In claim 93, replace the term, "claim 90" in line 1 with the term – claim 91 –.

8. Replace claim 94 with the following:

94. A method of replacing, in an isolated mouse embryonic stem (ES) cell, in whole or in part, an endogenous immunoglobulin variable region gene locus with part or all of a human immunoglobulin variable region gene locus comprising:

(a) using bacterial homologous recombination to genetically modify a cloned genomic fragment of an endogenous immunoglobulin variable region gene locus to create a first large targeting vector for use in eukaryotic cells (LTVEC), said LTVEC comprising a site-specific recombination site, a downstream homology arm containing a region immediately adjacent to, but not including, the J segments of the immunoglobulin variable gene locus region and an upstream homology arm within the variable gene locus, wherein the homology arms are larger than 20 kb and the site-specific recombination site is selected from one or more of loxP, lox511, and lox2272;

(b) using bacterial homologous recombination to genetically modify a cloned genomic fragment of an endogenous immunoglobulin variable region gene locus to create a second LTVEC comprising a site-specific recombination site, an upstream homology arm containing a region adjacent to the most distal V gene segment, but not containing any V gene segments of the immunoglobulin variable gene locus region and a downstream homology arm within the variable gene locus, wherein the homology arms are larger than 20 kb;

(c) introducing the first and second LTVECs into an isolated mouse ES cell;

(d) using a quantitative assay with a probe directed to an unmodified allele of the endogenous gene locus to detect reduced copy number of the unmodified allele

compared to that of a reference gene in the cell from (c) thereby indicating modification of allele (MOA) in the endogenous variable gene locus of the ES cell, wherein the site-specific recombination sites flank the endogenous variable region gene locus;

(e) creating a vector containing site-specific recombination sequences flanking all or part of a human immunoglobulin variable gene locus; and

(f) introducing the vector of (e) into the cell identified in (d) such that, through recombination, the endogenous immunoglobulin variable region gene locus is replaced, in whole or in part, with all or part of a human immunoglobulin variable gene locus.

Specification

In the specification, please amend as follows:

1. Page 1, line 4, insert the following text after "2001," – issued as U.S. Patent No. 6,596,541 on July 22, 2003, –.

2. Page 1, line 5, insert the following text after "2000," –issued as U.S. Patent No. 6,586,251 on July 1, 2003, –.

3. Page 19, line 16, insert the following text after "cDNA" – (SEQ ID NO: 5) and mouse OCR10 amino acid sequence (SEQ ID NO: 6) –.

4. Page 34, line 15, insert the following text after "3') – (SEQ ID NO: 1) –.

5. Page 34, line 16, insert the following text after "3')" – (SEQ ID NO: 2) –

6. Page 34, line 19, insert the following text after "3')" – (SEQ ID NO: 3) –

7. Page 34, line 20, insert the following text after "3')" – (SEQ ID NO: 4) –

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by

facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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